Original Article

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Thyroid Disorders in Children and Adolescents with Type 1 Diabetes Mellitus in Isfahan, Iran

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Abstract

Objective: Studies in different populations have shown great variation in the prevalence of thyroid diseases in patients with type 1 diabetes mellitus (T1DM). Our aim was to study the prevalence of thyroid disorders such as autoimmunity of thyroid (AIT), thyroid dysfunction, and goiter in children and adolescents with T1DM, compared with age- and sex-matched healthy controls in Isfahan.

Methods: One hundred patients with T1DM who were referred to Isfahan Endocrine and Metabolism Research Center and 184 healthy schoolchildren matched for age and sex were included. They were examined for goiter by two endocrinologists. Thyroid function test and serum thyroid antibodies (anti-TPO Ab and anti-Tg Ab) were measured.

Findings: The prevalence of subclinical hypothyroidism was high in both groups (18%). T1DM patients had lower frequency of goiter (21% vs. 38%, *P*=0.001), and higher prevalence of positive AIT (22% vs. 8%, *P*=0.001), anti-TPO Ab positivity (19.3% vs. 5.3%, *P*=0.000), and anti-Tg Ab (11.1% vs. 6.4%, *P*=0.1) in comparison with the control group. Being positive for AIT in diabetic patients meant an odds ratio of 5 (CI 95 %: 1.5-15.6) for thyroid dysfunction. There was no association between age, sex, duration of diabetes and HbA_{1C} with serum anti-TPO Ab and anti-Tg Ab concentrations in this group.

Conclusion: Our results demonstrated the high prevalence of AIT and thyroid dysfunction in patients with T1DM. We suggest regular thyroid function and antibody testing in these patients.

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Key Words: Type 1 diabetes mellitus; Autoimmune thyroid disease; Thyroid dysfunction disease; Goiter; Thyroid antibody

Introduction

Type 1 diabetes mellitus (T1DM) is the result of autoimmune destruction of beta cells in pancreas, which usually result in insulin deficiency. In two recent decades, the worldwide prevalence of diabetes mellitus (DM) has risen significantly from an estimated 30 million cases in 1985 to 177

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million in 2000[1]. It is estimated that 7.7% of Iranian adults aged 25–64 years, or 2 million adults, have DM, one-half of whom are undiagnosed[2]. There is a genetic predisposition toward T1DM, which also predisposes patients to other autoimmune diseases such as thyroid disease, celiac disease, adrenal insufficiency, vitiligo, alopecia, and gastric autoimmunity[3,4]. According to studies, 15-30% of T1DM patients have autoimmunity of thyroid (AIT)[5-8], 4-9% have celiac disease, and 0.5% have Addison's disease[8]. AIT as a more prevalent autoimmune disorder associating with T1DM is often clinically silent but it may progress to autoimmune thyroid disease (AITD), recognized as overt or subclinical hypothyroidism and hyperthyroidism[9].

Hypothyroidism can lead to growth delay, weight gain, menstrual abnormality, hyperlipidemia, and cardiovascular complications in diabetic patients[9].

Hyperthyroidism can worsen metabolic control of diabetes and increase its liability, often with a need for increased insulin dosage and increased chance of diabetic keto-acidosis[10,11].

AITD is detected most easily by measuring circulating antibodies against thyroid peroxidase (anti-TPO Ab) and thyroglobolin (anti-Tg Ab)[1]. Thyroid antibodies are more prevalent in T1DM patients compared with the general population. Studies have measured varying prevalence of between 3 and 50%, depending on the methodology of the study and patient's characteristics (age, sex, ethnicity, and genetic background)[4,12].

It should be noted that the prevalence of thyroid dysfunction in diabetic people is higher than in the general population, too. Studies have estimated a prevalence of 1-5% for overt hypothyroidism and 0.5-7% for thyrotoxicosis in young diabetic patients[4,13].

Because of the high prevalence of AIT and thyroid dysfunction in patients with T1DM and probable effects of thyroid disorders in metabolic control of these patients, there is a general agreement about screening of diabetics for thyroid antibodies and dysfunction. Despite this fact, there is still no consensus regarding screening of AIT and thyroid function in T1DM patients[14].

There are limited studies in Iran estimating the prevalence of thyroid disorders and AIT in patients with T1DM and most of them have been done in adults. The aim of this study was to determine the prevalence of thyroid disorders such as AIT, thyroid dysfunction, and goiter in children and adolescents with T1DM compared with age and sex matched healthy controls in Isfahan.

Subjects and Methods

This cross-sectional study was performed in Isfahan in 2009. Patients with T1DM who were under 18 years old and had a health profile in Isfahan Endocrine and Metabolism Research Centre with regular attending to the centre were enrolled into the study consecutively.

As a control group, healthy subjects matched for age and sex were selected with a multistage cluster random sampling from Isfahan school children [15].

We excluded individuals with history of recent or acute illness and history of taking drugs affecting thyroid function or size. A questionnaire was filled out for diabetic patients, which included information on the date of birth, sex, duration of diabetes, age at onset of DM, history of thyroid disease, drug history, and mean HbA_{1c} level during the past one year.

Goiter grading was performed by two endocrinologists according to WHO/UNICEF/ICCIDD classification [16]. Blood samples were taken for determination of serum level of thyroid stimulating hormone (TSH), total thyroxin (T4), anti-TPO Ab, and anti-Tg Ab. All samples were measured at the reference laboratory of the Isfahan Endocrine and Metabolism Research Center by the same person using the same method.

Serum T4 concentrations were measured using radio-immunoassay (Iran Kavoshyar Co., Tehran, Iran). Normal range for T4 level was 4.5-12 μg/dl. Serum TSH concentrations were determined with immunoradiometric assay (Iran Kavoshyar Co., Tehran, Iran). Normal range for TSH level was 0.3-3.9 mU/l. Overt hypothyroidism was defined as elevated TSH and low T4, subclinical hypothyroidism as elevated TSH and normal T4, overt hyperthyroidism as low TSH and elevated

T4 and subclinical hyperthyroidism as low TSH and normal T4.

Serum anti-TPO Ab and anti-Tg Ab were measured by Rapid ELISA (Genesis Diagnostics, Littleport, UK). Anti-Tg Ab and anti-TPO Ab concentrations more than 100 IU/ml and 75 IU/ml, respectively, were considered positive. Positivity of at least one antibody was considered as having AIT.

Quantitative variables are presented as mean±SD and range. Independent sample t-test was used to compare normally distributed data in different groups. Mann-Whitney U-test was used when quantitative variables were not normally distributed. Qualitative variables were compared by Chi-square test. Correlation between quantitative variables was calculated by Spearman's rank correlation coefficient. *P*-value less than 0.05 was considered statistically significant. All analysis was performed using SPSS version 15 (SPSS Corp, Chicago, IL, USA).

Written informed consent was obtained from all children's parents. The study was approved by the local ethics committee of the Endocrine and Metabolism Research Center.

Findings

One hundred children and adolescents with T1DM and 284 controls were enrolled into the study. No significant differences were found between groups according to age and sex. Table 1 demonstrates the demographic characteristics of the study population.

Serum TSH concentration was abnormal in 19 (19%) children with T1DM and 53 (18.7%) children of the control group (*P*=0.90). Eighteen (18%) patients with T1DM and 51 (51%) individuals in the control group had subclinical hypothyroidism. Subclinical hyperthyroidism was detected in one (1%) patient with T1DM and two (0.7%) children in the control group (*P*=0.35). Overt thyroid disease was not identified in the two groups. There were no significant differences between diabetic patients and non-diabetic ones regarding mean serum TSH (2.59±1.32 vs. 2.78±1.55 mU/l, *P*=0.30) and T4 (10.88±16 vs. 8.55±1.52 µg/dl, *P*=0.10) con-centrations.

The prevalence of goiter was higher in the control group (38% vs. 21%, *P*=0.001). There was no significant difference between the prevalence of goiter and thyroid dysfunction in T1DM patients and non-diabetic participants based on different sex group.

The mean serum anti-TPO Ab and anti-Tg Ab in diabetic children were three times higher than those in the control groups (Table 2).

Anti-TPO Ab was positive in 16 out of 83 (19.3%) patients and 15 out of 284 (5.3%) non-diabetic participants (*P*=0.000). This difference was not significant according to positivity for anti-Tg Ab (11% in T1DM children vs. 6.4% in the control group, *P*=0.10). The prevalence of AIT in diabetic children was 2.5 times higher than that in the control group (*P*=0.001) (Table 2).

Dividing diabetic children into two groups according to the presence of thyroid antibodies, there were no significant differences between the groups in age, sex, age at onset of diabetes, duration of diabetes, HbA_{1c}, serum TSH, and T4 concentration (*P*>0.05). Diabetic patients with AIT had higher prevalence of thyroid dysfunction (Table 3). The chance for having thyroid dysfunction in diabetic children who had AIT was five times higher than those who had not AIT(Odds ratio: 5, CI 95%: 1.5-15.6%, *P*=0.008).

The prevalence of goiter in diabetic children

Table 1: Demographic characteristics of the individuals with and without T1DM

	Type 1 diabetics n=100	Non-diabetic controls n=284	*P* value
Age; years	10.64 ±2.56 (6-14)	10.39 ±0.87 (9-13)	NS*
Sex (female/male)	59/41	159/125	NS
Duration of DM; years	4.18±2.42 (1-14)	-	-
Age at onset of DM; years	6.94±3.15 (1-13)	-	-
HbA_{1c} (%)	8.32 ±1.56 (5.3-14.3)	-	-

Quantitative variables are presented as mean (standard deviation) and range / NS: Not Significant

Table 2: Thyroid antibodies concentration and thyroid autoimmunity in individuals with and without T1DM

		Type 1 diabetics n=83	Non-diabetic controls n=284	*P* value
Anti-TPO Ab (IU/m)	**Mean (SD)**	96.73 (330.89)	31.27 (120.76)	0.007
	Range	0.3-2671	1.1-1213	
Anti-Tg Ab (IU/m)	**Mean (SD)**	243.73 (1279.00)	71.57 (377.40)	<0.001
	Range	0.1-9000	0.5-4134	
Anti-TPO Ab positivity (%)		16 (19.3%)	15 (5.3%)	<0.001
Anti-Tg Ab positivity (%)		9 (11%)	18 (6.4%)	NS
Anti-TPO and Anti-Tg Ab positivity (%)		7 (8.4%)	10 (3.5%)	NS
AIT (%)		18 (21.7%)	23 (8.09%)	0.001

SD: standard deviation / NS: Not Significant

with AIT was higher than that in diabetics without AIT. However, this difference was not statistically significant (Table 3).

There was no correlation between age, duration of diabetes, and age at onset of diabetes on the one hand, and anti-TPO Ab and anti-Tg Ab, on the other hand, in diabetics. A positive correlation was found between anti-TPO Ab and anti-Tg Ab concentrations in these patients (r=0.5, P<0.001).

Discussion

In the present study, we showed that children with T1DM had higher levels of both anti-TPO Ab and anti-Tg Ab compared with healthy ones.

Also, T1DM children had higher prevalence of positive anti-TPO Ab than non-diabetic individuals.

It has been shown that T1DM has strong relationship with autoimmune disorders such as pernicious anemia, celiac disease, and idiopathic adrenal insufficiency. AIT is the most prevalent autoimmune disorders associated with T1DM [13,17]. The reason for the high prevalence of some autoimmune disorders in these patients still remains undetermined. It may be due to a generally increased tendency to react against certain antigens, or a genetically impaired ability to acquire tolerance to some autoantigens, or certain common antigens present in the tissues of individuals prone to autoimmune diseases [18].

According to some studies, common genetic determinants, mainly human leukocyte antigen

Table 3: Clinical characteristics of diabetic children with and without AIT

	Diabetics with AIT n=18	Diabetics without AIT n=65	*P* value
Age, years	10.83 (2.40)	10.52 (2.56)	NS
Sex (female/male)	11:7	36:29	NS
Duration of DM, years	4.06 (2.20)	3.98 (2.42)	NS
Age at onset of DM, years	7.06 (2.87)	7.29 (3.31)	NS
HbA1c (%)	8.88 (1.56)	8.24 (1.50)	NS
TSH (mU/l)	3.09 (1.73)	2.60 (1.16)	NS
T4 (µg/dl)	9.05 (2.51)	12.10 (19.95)	NS
Anti-TPO Ab (IU/m)	395.30 (637.73)	14.05 (15.70)	<0.001
Anti-Tg Ab (IU/m)	1089.35 (2686.24)	19.11 (20.90)	<0.001
Number of patients with Thyroid dysfunction (%)	8 (44.4%)	9 (14.1%)	0.005
Subclinical hypothyroidism	7 (38.8%)	9 (13.8%)	0.02
Subclinical hyperthyroidism	1 (5.5%)	0	NS
Number of patients with goiter (%)	7 (38.8%)	11 (16.9%)	NS

SD: standard deviation / NS: Not Significant

(HLA) risk alleles[19,20] or other genes outside the HLA region (i.e., CTLA4 gene and PTPN22 gene), could play a role[21,22] in the occurrence of AIT in T1DM patients. Moreover, environmental factors such as stress, infection, trauma, smoking, drugs, and nutrition (especially increased iodine intake) seem to be involved[23].

Both T1DM and AIT are organ-specific T-cell mediated diseases, and have similar patho-genesis, which involves T-cell infiltration resulting in dysfunction of the target organ[23].

In the present study, the prevalence of positivity for anti-TPO Ab, anti-Tg Ab, and the prevalence of positivity for both antibodies and AIT (at least one positive Ab) in children with T1DM was 19, 11, 8.4, 22%, respectively, which was higher than those in non-diabetic individuals. In other studies, the prevalence of positive anti-TPO Ab in T1DM patients was reported to be 5.5-46.2%. The prevalence of high anti-Tg Ab in these patients ranged from 2.1 to 40%. In those studies, the prevalence of AIT in T1DM and healthy individuals was reported to be 11-46% and 1.4-11%, respectively. The wide range of these data can be explained by the difference in genetic factors, age, and sex of the studied population[24], as well as the different methods for measurement of antibodies[9]. Most studies that reported the low prevalence of AIT were conducted 1-2 decades ago, showing the lower sensitivity of the laboratory tests. Meanwhile, this finding might be a result of a real increase in the prevalence of AIT during the recent decades[9]. Epidemiologic studies have shown higher incidence of AIT after elimination of iodine deficiency in endemic areas[23].

In previous studies in Iran, the prevalence of positive anti-TPO Ab and anti-Tg Ab in T1DM patients were reported to be 27-39.6% and 27-34%, respectively[17,25-27]. The lower prevalence of AIT in our study could be explained by the different age group of studied individuals in our study. The previous studies in Iran were conducted in adult population or had recruited some adults. However, the present study was conducted on children and showed comparable results with other studies performed in similar age group in northwestern part of Iran[24] and other countries[28]. Age dependent increase of AIT incidence has previously been described[28].

The prevalence of clinical and subclinical thyroid dysfunction in T1DM patients is suggested to be 13.4-20%[25], whilst the prevalence of hypothyroidism and hyper-thyroidism in the normal population is 5-10% and 1%, respectively[8]. In the present study, there was no case of clinical thyroid dysfunction. However, subclinical hypothyroidism was present in 18% of both T1DM patients and the control group. In our study, the prevalence of subclinical hyperthyroidism in T1DM patients and non-diabetic subjects was 1% and 0.7%, respectively, which is consistent with the findings of previous studies[4]. We found that diabetic patients with AIT had higher prevalence of subclinical hypothyroidism than diabetic patients without AIT (38.8% vs. 13.8%), which was statistically significant. Also, there was a positive correlation between thyroid dysfunction and AIT (data not shown). Therefore, the higher prevalence of subclinical hypothyroidism in T1DM patients could be explained by the high prevalence of AIT (22%) in these patients. As well as AIT, iodine deficiency can cause clinical or subclinical hypothyroidism[1]. Unfortunately, we did not evaluate iodine status of the studied population and as a result, we could not investigate the role of iodine deficiency in the high prevalence of subclinical hypothyroidism.

In the present study, the prevalence of goiter in T1DM and non-diabetic individuals was 21 % and 38%, respectively. The lower prevalence of goiter in T1DM patients in comparison with that in non-diabetic ones is in contrast with previous studies, which showed no difference in goiter prevalence between T1DM patients and control group[29-31] or higher prevalence of goiter in patients with T1DM[32,33]. Studies that showed higher thyroid volume and goiter prevalence in T1DM patients attributed this finding to the higher incidence of AIT in T1DM[34]. However, we showed the higher prevalence of goiter in T1DM patients with AIT (38.8%) than in patients without AIT (17%). As stated before, we did not evaluate the iodine deficiency as a possible contributor of goiter. The higher levels of urinary iodine concentration in T1DM patients was previously reported[34]. We classified children into goitrous and nongoitrous groups by inspection and palpation. The sensitivity and specificity of palpation is poor and

it would be more accurate if we use thyroid ultrasonography to determine goiter size.

In our study, the prevalence of AIT in female patients with T1DM was higher than that in male T1DM patients. In the control group, the prevalence of AIT in male patients was higher than that in female ones. However, it should be stated that the differences were not statistically significant. Many studies found higher prevalence of positive thyroid autoantibodies in females[12,35,36] and some studies reported similar prevalence in both genders[37,38].

In agreement with previous studies[6,39,40], in the current study, we found no relationship between HbA_{1c}, as a measure of metabolic control in diabetic patients, and AIT or thyroid dysfunction.

Conclusion

Children and adolescents with T1DM had higher levels of thyroid autoantibodies, higher prevalence of AIT, and subclinical hypothyroidism than non-diabetic ones. It seems beneficial to measure thyroid function indices and thyroid antibodies in patients with T1DM, regularly.

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Conflict of Interest: None

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